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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/448,633	11/24/1999	AI-PING WEI	53091USA8B	5266

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EXAMINER

MORAN, MARJORIE A

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 12/04/2001

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/448,633

Applicant(s)

WEI ET AL.

Examiner

Morjorie Moran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1a) ☒ Responsive to communication(s) filed on 17 September 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 21 is/are rejected.
- 7) ☒ Claim(s) 20 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: detailed action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

In view of the amendments filed 9/17/01, the rejections made under 35 USC 112 are hereby withdrawn.

Claim Rejections - 35 USC § 102

Claims 1, 3-4, 6-8, 10, 12-13, and 15-18 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over GARMAN *et al.* (GB 2278356) with support from ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701) and WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), and TSIEN *et al.* (US 5,741,657).

Applicant's arguments filed 9/17/01 have been fully considered but they are not persuasive. In response to applicant's argument that GARMAN is not anticipatory as GARMAN does not specifically teach dimerization, applicant's attention is drawn to MPEP 2131.01, which states:

"Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:

- (A) Prove the primary reference contains an "enabled disclosure; "
- (B) Explain the meaning of a term used in the primary reference; or
- (C) Show that a characteristic not disclosed in the reference is inherent."

MPEP 2131.01 also states that an extra reference or evidence can be used to show an inherent characteristic of the thing taught by the primary reference:

"To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."

As previously set forth in the office action of 6/14/01, ROHATGI provides support that both fluorescein and tetramethylrhodamine are capable of dye-stacking (p. 1696 and 1699) and WEI provides support that fluorescein and tetramethylrhodamine attached to a peptide can interact to "essentially" self-quench the fluorescence groups (p. 1503, Figure 3A). WEI specifically teaches that fluorescein and tetramethylrhodamine attached to either end of a peptide undergo dye dimerization (page 1503). TSIEN provides further support that hydrophobic donor and acceptor fluorophores can stack (dimerize) when separated by a short flexible linker in a polar solvent (col. 18, lines 28-34), and provides multiple examples of fluorescein stacking with other xanthene dyes when attached to a short flexible linker. TSIEN specifically teaches an enzyme substrate comprising a flexible linker with fluorescein on one end and tetramethylrhodamine on the other (TSIEN's RCF), wherein the dyes stack to become quenched, and fluoresce upon cleavage of the substrate with the enzyme (col. 25, lines 3-8). See also col. 30, lines 10-21 and col. 34, lines 11-20. TSIEN teaches that dye dimerization, or stacking of dyes, can be distinguished from donor and acceptor pairs which do not stack (col. 42, lines 20-68). Given the preponderance of evidence in the prior art supporting dye stacking between fluorescein and tetramethylrhodamine when separated by a short linker in a polar

solvent, one skilled in the art would reasonably conclude that the fluorescein and tetramethylrhodamine attached to a peptide substrate in aqueous buffer (water or Tris-HCl), as taught by GARMAN (see e.g. pp. 14-15) would inherently be stacked when exhibiting the dye quenching taught by GARMAN. In response to the argument that GARMAN teaches resonance energy transfer, which is different from dimerization, it is noted that the two are not mutually exclusive. WEI specifically teaches that quenching efficiency of a dual labeled peptide (FpepT) is probably due to BOTH dimerization and energy transfer (page 1503, left column), and TSIEN teaches that as dyes in a dual labeled substrate diffuse away from each, "stacking and energy transfer are disrupted" (col. 18, lines 40-43), thus suggesting that stacking and energy transfer are mutual.

As decided in *In re Best, Bolton, and Shaw*, 195 USPQ 430, 431 (CCPA 1977), "Mere recitation of newly-discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art; Patent Office can require applicant to prove that subject matter shown to be in prior art does not possess characteristic relied on where it has reason to believe that functional limitation asserted to be critical for establishing novelty in claimed subject matter may be inherent characteristic of prior art; this burden of proof is applicable to product and process claims reasonably considered as possessing allegedly inherent characteristics." Further, "Patent and Trademark Office can require applicant to prove that prior art products do not necessarily or inherently possess characteristics of his claimed product where claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant where rejection is based on inherency under 35 U.S.C. 102, or on prima facie obviousness under 35 U.S.C. 103, jointly or alternatively, and Patent and Trademark

Office's inability to manufacture products or to obtain and compare prior art products evidences fairness of this rejection; there is nothing inconsistent in concurrent rejection for obviousness under 35 U.S.C. 103 and for anticipation by inherency under 35 U.S.C. 102."

Applicant has not provided any evidence that the fluorescent groups attached to the peptide substrate of GARMAN would NOT inherently stack under the conditions taught by GARMAN. Absent convincing evidence to the contrary, the examiner maintains that GARMAN's peptide substrate and method meet all of the limitations of the instant claims, as the fluorescent groups taught by GARMAN would inherently stack to self-quench, as supported by ROHATGI, WEI, and TSIEN.

Claim Rejections - 35 USC § 103

Claims 1-8 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701), WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), and TSIEN *et al.* (US 5,741,657), and in view of KOMORIYA *et al.* (US 5,714,342).

Claims 9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701), WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506) and TSIEN *et al.* (US 5,741,657) in view of KOMORIYA *et al.* (US 5,714,342), as applied to claims 1-8 and 10-18 above, and further in view of HEATH, JR. *et al.* (US 5,235,039).

Applicant's arguments filed 9/17/01 with regard to claims 1-19 have been fully considered but they are not persuasive. Applicant repeats arguments that GARMAN does not teach dimerization, therefore it would not have been obvious to have combined GARMAN's peptide substrate with the dimerizing dyes of KOMORIYA, or with the dimerizing dyes of

KOMORIAY in combination with the teachings of HEATH. The examiner maintains that GARMAN teaches dimerizing dyes, as set forth above, and therefore maintains that it would have been obvious to have combined the teachings of GARMAN and KOMORIYA or GARMAN, KOMORIYA and HEATH for the reasons and motivations previously set forth.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over GARMAN *et al.* (GB 2278356) as supported by ROHATGI *et al.* (J. Phys. Chem. (6/1966) vol. 70 (6), pages 1695-1701), WEI *et al.* (Anal. Chem. (5/1994), vol. 66 (9), pages 1500-1506), and TSIEH *et al.* (US 5,741,657), and in view of MANAFI *et al.* (Microbiol. Reviews (9/1991), vol. 55 (3), pages 335-348).

Applicant's arguments filed 9/17/01 have been fully considered but they are not persuasive. Applicant repeats arguments that GARMAN does not teach dimerization, and argues that HEATH does not supply the lack of GARMAN's teaching. The examiner maintains that GARMAN teaches dimerizing dyes, as set forth above, and therefore maintains that it would have been obvious to have combined the teachings of GARMAN and HEATH for the reasons and motivations previously set forth.

Allowable Subject Matter

Claim 20 is again objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The following is a statement of reasons for the indication of allowable subject matter:
The prior art does not teach the structure recited in claim 20. The prior art does not teach any

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motivation to pick the particular amino acid sequence recited in claim 20 as the peptide portion of the claimed substrate, nor does the prior art teach the claimed sequence as part of any other (e.g. larger) protease substrate, therefore claim 20 is not suggested by the prior art.

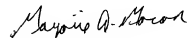
Conclusion

Claims 1-19 and 21 are rejected; claim 21 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marjorie A. Moran whose telephone number is (703) 305-2363. The examiner can normally be reached on Monday to Friday, 7:30 am to 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (703) 308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to a patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.



Marjorie A. Moran
Patent Examiner
November 30, 2001